REMARKS

1. Introduction

In the Office Action mailed February 9, 2004, the Examiner rejected claims 1-4 and 8 under 35 U.S.C. 103(a) as being unpatentable over Nasir et al., *Combinatorial Chemistry & High Throughput Screening* ("Nasir") in view of Dixon et al., U.S. Patent No. 4,835,100 ("Dixon") and further in view of Dhar et al., U.S. Pub. No. 2002/0110803 ("Dhar"). The Examiner rejected claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Nasir, in view of Dixon and further in view of Dhar and further in view of Michel et al., U.S. Patent No. 5,741,654 ("Michel"). The Examiner rejected claims 9-10 under 35 U.S.C. 103(a) as being unpatentable over Nasir, in view of Dixon and further in view of Dhar and further in view of McMahon et al., U.S. Patent No. 5,166,078 ("McMahon"). The Examiner rejected claims 11-18 as being unpatentable over Nasir, in view of Dhar and further in view of Dixon.

For the reasons set forth below, Applicants respectfully request reconsideration and allowance of the claims.

2. Response to Rejections

With respect to the Examiner's rejections of the claims under § 103, Applicants submit that the Examiner has not established a *prima facie* case of obviousness, for the reasons set forth in Applicants' previously-filed "Response to Office Action Mailed October 8, 2002" and "Response to Office Action Mailed May 15, 2003." Rather than repeat those arguments in their entirety, Applicants emphasize the following points.

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a. The Examiner can point to no prior art teaching of a "tracer comprising an aflatoxin oxime conjugated to a fluorophore ... able to bind to said antibody to produce a detectable change in fluorescence polarization."

The Examiner has not adequately addressed the special property of being able to bind to an antibody specific for aflatoxin "to produce a detectable change in fluorescence polarization," as recited in claims 1 and 11. In order to establish a *prima facie* case of obviousness, there must be a prior art teaching of a reasonable expectation of success, and the prior art must teach or suggest all the claim limitations. *See* MPEP § 2143. However, the Examiner has not satisfied either of these elements. The Examiner has not identified any prior art teaching that an aflatoxin oxime conjugated to a fluorophore would still be able to bind to an antibody specific for aflatoxin. Nor has the Examiner identified any prior art teaching that any binding would produce a detectable change in fluorescence polarization. In fact, Nasir teaches that even if binding occurs little polarization shift may be observed, due to a phenomenon called the "propeller effect." *See* Nasir, p. 180. As a result, the Examiner has not established a *prima facie* case of obviousness.

In the Office Action mailed February 9, 2004, the Examiner states that the above argument is not persuasive because "the primary reference of Nasir et al teaches this feature," i.e., the special property of being able to bind to an antibody to produce a detectable change in fluorescence polarization. In fact, the Nasir reference ***cannot possibly*** teach this feature because, as the Examiner has admitted, the Nasir reference "does not point out if the particular mycotoxin used was an aflatoxin." Indeed, it is because the Nasir reference makes no such mention of aflatoxin that the Examiner has relied on other references, i.e., Dixon and Dhar. Given this fact, it is entirely inconsistent for the Examiner to then argue that the primary reference of Nasir

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somehow teaches the special property of being able to bind to an antibody specific for aflatoxin to produce a detectable change in fluorescence polarization.

Moreover, the statements in Nasir regarding mycotoxin research cannot be interpreted as teaching that any specific mycotoxin, e.g., aflatoxin, when conjugated to a fluorophore, would actually have the required property of being able to bind to an antibody to produce a detectable change in fluorescence. This is because there are many different types of mycotoxins other than aflatoxins, e.g., trichothecenes, cyclopiazonic acid, fumonisins, ochratoxin, patulin, zearalenone, ergot alkaloid, fusarochromanone, PR toxin, rubratoxin, and sterigmatocystin, and these mycotoxins "have a wide array of chemical structures." (see Pestka, paragraph 1 on p. 120). Given the significant number of different types of mycotoxins, and the wide array of chemical structures that mycotoxins have, the statements in Nasir regarding mycotoxins cannot be interpreted as teaching a reasonable expectation that fluorescence polarization (FP) assays would succeed for each and every type of mycotoxin. Indeed, while the section in Nasir that refers to mycotoxins cites a number of articles, none of the cited articles actually relate to FP assays for mycotoxins, and Nasir does not report any actual results for FP assays for mycotoxins. Thus, the skilled artisan would have recognized from Nasir only that fluorescence polarization was "a technique of great potential in this area of research," not that FP assays could be used successfully for any particular mycotoxin.

b. The Nasir reference teaches away from the claimed invention

Even if the statements in the Nasir reference regarding mycotoxin research could be applied to aflatoxin specifically, the statements actually teach away from the claimed invention. In particular, the Nasir reference states:

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> A mycotoxin antigen of interest is labeled with a suitable fluorescent molecule (tracer).

(Nasir, p. 182, col. 1). One following this statement would probably try to label aflatoxin with a fluorophore. Indeed, this is what the inventors tried to do -- but they found that it did not work. (Nasir Decl., ¶ 5). It was not until the inventors took the innovative approach of conjugating a fluorophore to an aflatoxin oxime instead that they were able to develop a tracer. (Nasir Decl., ¶ 6). Even then, they did not know whether the tracer would be able to bind to the antibody to produce a detectable change in fluorescence polarization until the tracer was tested. (Nasir Decl., ¶ 6). Moreover, for many fluorophores, there was no appreciable change in polarization values upon reaction to the antibody solution. (Nasir Decl., ¶ 6).

Thus, the claims require a tracer comprising an aflatoxin ***oxime*** conjugated to a fluorophore, with the result that the Nasir reference actually teaches away from the claimed invention. Clearly, the Nasir reference cannot be combined with other references to support an obviousness rejection. *See* MPEP § 2145(X)(D)(2) ("It is improper to combine references where the references teach away from their combination.").

Nonetheless, the Examiner argues that Dhar teaches the use of an aflatoxin oxime. In fact, Dhar teaches using an aflatoxin oxime in order to attach an enzyme label, not to attach a fluorescent label. The Examiner has not identified any reason why one of ordinary skill in the art would have gone against the statement in Nasir and used an aflatoxin oxime instead – particularly since Dhar did not prepare the oxime for the purpose of fluorophore conjugation. Moreover, the Examiner has not identified any prior art teaching that an aflatoxin oxime conjugated to a fluorophore would be able to bind to an antibody to produce a detectable change in fluorescence polarization.

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c. Nasir and Dhar teach away from their combination

Dhar teaches away from Applicants' invention by teaching a heterogeneous assay. In particular, for the aflatoxin B1 assay of Example 1, Dhar teaches immobilizing the antibody to aflatoxin B1 in a membrane (Dhar, ¶¶ 67, 98). In contrast to this **heterogeneous** assay taught by Dhar, the claims refer to **homogeneous** assays. Because Dhar teaches away from Applicants' invention, Dhar cannot be combined with other references to support an obviousness rejection. *See* MPEP § 2145(X)(D)(2) ("It is improper to combine references where the references teach away from their combination.").

In response, the Examiner has argued that "FP assays does not exclude the teaching of heterogeneous assays." In fact, the claims ***are*** specific to homogeneous assays. Claim 1 recites "[a] homogenous assay ..." and claim 11 recites "in a homogeneous assay." Moreover, the Nasir reference makes clear that antibody-antigen interactions can differ depending on whether the assay is homogeneous or heterogeneous:

> In ELISA compounds adsorbed to the solid phase may have different affinities than in solution. The adsorbed antigens may denature with time [29], and at the solid phase steric hindrance might occur for larger molecules [30].

(Nasir, p. 191, col. 2). Thus, Nasir teaches away from reliance on the characteristics of heterogeneous assays, such as in Dhar. Accordingly, the Nasir and Dhar references teach away from their combination.

For the reasons set forth above, Applicants submit that the claims are allowable over the prior art of record, including Nasir, Dixon, and Dhar.

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3. Conclusion

Applicants submit that the present application is now in condition for allowance and notice to that effect is hereby requested. Should the Examiner feel that further dialog would advance the subject application to issuance, the Examiner is invited to telephone the undersigned at any time at (312) 913-0001.

Respectfully submitted,

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